REMARKS

The Office action of December 23, 2003 is hereby acknowledged with appreciation. Claims 29-61 remain pending in the application. Claims 29-44, 47-49, 52-55 and 60-61, relating to restriction Group I, are withdrawn from consideration by the Office. The Applicants inquire as to the Office basis for excluding Claims 47-49 from consideration. These claims were identified with original Group II, claims 45-51 and 56-59, and are drawn to the elected method of preparing a membrane fraction pharmaceutical composition for the treatment of a cancer. Moreover, these claims are drawn to subspecies of the elected species, namely, chemotherapy.

With regard to the Applicant's claim for foreign priority based on the French application, it was noted that the Office has not received a certified copy of the translation of the application. The Applicants note this non-statutory request. The required English translation of International application number PCT/FR00/00623 was provided and acknowledged in the USPTO Form PCT/DO/EO/903 of September 14, 2001. With this Response and Amendment, the Applicants comply with the Office non-statutory request and hereby provide a certified copy of the English translation of the French priority 99/03,154 03/15/1999 filed May 8, 2000.

Moving on, Claims 45-46, 50-51 and 56-59 are rejected under 35 U.S.C, § 101 for improper definition of a process. With this Response and Amendment, the claims are converted from the European "use" language to accepted U.S. "method" claims. The Applicants submit that these amendments obviate the rejection.

Claims 45-46, 50-51 and 56-59 are rejected under 35 U.S.C, § 112, first paragraph, as failing to comply with the enablement requirement. It is the Office position that the Specification fails to show how proteoglycans from a Gram-negative bacterium are used for the preparation of an anticancer pharmaceutical preparation for administration, optionally in combination with an anticancer treatment, to treat malignant melanomas. The Specification speaks to the treatment of cancer, making reference to Bacille Calmette Guérin therapy (page 2) wherein bladder cancers are treated and prevented with agents which enhance the immune system. This method of treating and preventing the recurrence of bladder cancers is routinely practiced by those skilled in the art. The efficacy of Bacille Calmette Guérin therapy for the treatment of bladder cancer is attributed to the immunostimulatory properties including upregulation of cytokines and cell activation with amplification of cytotoxic populations.

However, treatment with Bacille Calmette Guérin therapy is limited due to the high side effect profile and is also contraindicated in certain patient populations. Therefore, effective immunotherapies with enhanced safety profiles are desired. The instant invention is drawn to the immunostimulatory properties of membrane fractions from *Klebsiella pneumoniae* comprising proteoglycans. As noted by the Office, the immunostimulatory properties of the *K. pneumoniae* FMKp include proliferation of PBMC's, which include lymphocytes, monocytes, and natural killer cells, which elicit secretory cytokine responses. Such response, as evaluated in monocytes, is evidenced by the enhanced production of cytokines TNF-α and IL-12 upon stimulation with FMKp. The contribution of the immune response to the treatment of bladder cancers is understood by those skilled in the art and is a strategy currently being explored for the treatment of various cancers including liver, prostate and osteosarcomas. Specificational support for those cancers in which it is known that host immunological defense mechanisms play an important role in tumor progression is found on page 13, lines 17-21. Therefore, immunostimulation by administration of proteoglycans of the instant invention may be understood to enhance conventional anti-cancer

therapies. Those skilled in the art recognize that effective antitumor responses are mediated by the cells of the immune system, particularly T lymphocytes and natural killer cells. Those who practice in the art of biological therapy recognize that enhanced immune cell proliferation and cytokine secretion, particularly TNF-α and IL-12, as a result of stimulation with FMKp provides an effective means of eliciting an antitumor response.

Additionally, the Office provides a reference to Burton, RC (CA Cancer J Clin. 2000, 50:209-213) which discloses the biological treatment of malignant melanoma with immunotherapy by administration of interferon-α. Burton discloses that chemotherapy for the treatment of melanoma has not improved and suggests that biological agents hold promise since melanoma is immunogenic and the immune system can respond to it. Burton recites, "Melanoma has always been one of the most promising cancers for trials of immunotherapy." The reference also discloses that immuostimulants, such as interferon-α, are currently in development for the treatment of malignant melanoma, and that the results from clinical trials of this new approach are promising. Compositions which elicit an enhanced immune response, such as FMKp, provide alternative type of immunotherapy to that which is currently contemplated for the treatment of melanoma, as well as for other cancers. Stimulation of the immune response by administration of a composition comprising FMKp is found in Examples 2 and 3 of the Specification. Support and guidance for required dosage to elicit PBMC proliferation as well as reproducible stimulation of cytokines TNF-α and IL-12, are disclosed. The Applicants submit that the Specification is sufficiently enabling to those skilled in the art for the stimulation and measurement of such response.

Moreover, the Office cites the reference Yen-Maguire, et al., (U.S. Patent No. 5,242,806) which discloses methods for conducting cytotoxicity assays on tumor cells which reference was included as an example of the current state of the art. For evaluation of the immunotherapeutic properties of the FMKp

protein, alone or in combination with conventional anti-cancer treatments, the Applicants rely on the present state of the art in oncology wherein treatment with combination therapies, clinical trials, and analysis of efficacy are routinely practiced by those skilled in the art and thereby, further provide an enabling disclosure. Conventional cancer therapies, practiced by those skilled in the art, may be enhanced by the immunostimulatory properties of the instant FMKp membrane fraction. The Applicants submit that one skilled in the art is familiar with representative techniques for evaluating cytotoxicity, such as those disclosed by Yen-Maguire, et al., and that clinical trials for the evaluation of the efficacy of immunotherapy is practiced by those skilled in the art as disclosed in Burton and by reference to Bacille Calmette Guérin therapy. The Applicants submit that those who understand the contribution of the immune response to cancer treatment and those skilled in the art of immunotherapy recognize that the Specification provides an enabling disclosure.

Claims 45-46, 50-51 and 56-59 are rejected under 35 U.S.C. § 112, second paragraph, for failing to claim with particularity. It is the Office position that the language "intended to be administered" renders the claims indefinite. With this Response and Amendment, the Applicants amend the European "use" claims to conform to U.S. "method" claims, thereby obviating this objection to claim language.

The Office rejects claims 45-46, 50-51 and 56-59 under 35 U.S.C. § 103(a) as being obvious in view of the Shyjan, AW (U.S. Patent 5, 674,739) disclosure. The reference disclosure is directed to an endogenous mammalian tumor progression inhibitor which is down-regulated in tumor cells, whereby low expression levels correlate with high metastatic potential. The disclosed utility is the use of the protein as a biomarker or prognostic indicator for assessing the metastatic potential of tumorigenic cells. Therefore, the diagnosis, prevention, and treatment of tumor progression can be facilitated by quantification of the relative expression levels of this protein. The reference discloses that the

efficacy of anticancer treatments can be evaluated based upon quantitation of the relative expression levels of this particular protein in biopsies or tumor cells.

The Office concludes that it would be obvious to substitute the tumor progression inhibitor of Shyjan for the proteoglycan of the instant invention to achieve a combination therapy for the treatment of malignant melanoma. This is, of course, not tenable since the instant invention relates to the immunostimulatory effects of proteoglycans to treat cancers and/or enhance chemotherapy regimes.

The Office is relying on improper hindsight reasoning. The fact that "the person of ordinary skill in the art would utilize all available options for designing enhanced methods for...preventing and/or treating malignant melanoma..." is laudable, but not relevant to the instant enquiry. The patentability question pertains to the question whether one skilled in the art actually has taught or suggested combination of the prior art disclosure of record to formulate a therapy which is the instant invention. The Office has not demonstrated this to be true.

Consequently, it is the Applicant's position that it is not obvious from the Shyjan disclosure that a proteoglycan, derived from a membrane fraction of a prokaryotic microorganism, *Klebsiella pneumoniae,* through its immunostimulatory effects, could enhance the therapeutic potential of chemotherapeutic agents or enhance an antitumor response. Absent some teaching in the prior art which may be considered to make some connection between these divergent technologies, the Applicants submit that the Office has not made their *prima facie* argument for obviousness.

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Accordingly, entry of the present amendment and accompanying Certified Translation of the Priority Document, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,
THE FIRM OF HUESCHEN AND SAGE

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Enclosure: Listing of Claims and Certified English Translation of French Priority 99/03,154.

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THE COMMISSIONER IS HEREBY AUTHORIZED TO CHARGE ANY FURTHER OR ADDITIONAL FEES WHICH MAY BE REQUIRED (DUE TO OMISSION, DEFICIENCY, OR OTHERWISE), OR TO CREDIT ANY OVERPAYMENT, TO DEPOSIT ACCOUNT NO. 08,3220.